REMARKS/ARGUMENTS

Status of the Claims

Claims 19-23 and 26-36 are pending. Claims 19-22 and 29 are rejected. Claims 24 and 25 are canceled.

Applicants believe that claims 26-28 and 30-36 are withdrawn, and thus claims 19-23 and 29 are under reconsideration. The Office Action Summary states that "claims 23, 26-28 and 30-36 are withdrawn," while page 2 of the Office Action states that "claims 21, 22, 26-28 and 30-36 are withdrawn. . . . Claims 19-22 and 29 are readable upon the elected invention and are examined herein on the merits for patentability." Applicants respectfully request that the Examiner clarify the claims under reconsideration. Applicants note that claim 23 reads on a compound in which X_1 is a p-aminobenzyl moiety, which was part of the species elected on June 20, 2007.

Claims 19, 20 and 31 have been amended for clarity.

Claims 19 and 20 have also been amended to recite that the *q* value of said MRI agent is increased. Support for the amendment can be found, for example, on page 7, lines 28-33 of the specification.

Rejection under 35 USC 112

The Examiner has rejected claims 19 and 21 under 35 USC 112 for allegedly failing to comply with the written description requirement. The Examiner alleges that "Applicant's limited disclosure of such a small number of representative amino acid sequences does not provide support that applicant was in possession of a reasonable number of species of the claimed genius to substantiate claiming such a broad genus." Applicants disagree.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP 2163(I). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Id.* (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)).

Claim 19 recites a structure having a $-(Y_1)_n$-Ala-Leu-$(Y_2)_m$ moiety. Thus, all of the species of claim 19 share at least one common feature, namely, an -Ala-Leu- moiety that is part of a possibly bigger peptide moiety. The specification on page 24, lines 12-22 discloses that Y_1 and Y_2 refer to independently chosen amino acids, which are well understood in the art. The specification discloses that Y_1 and Y_2 may be used to form peptide moieties that are the same or different or that may have some amino acids in common. As stated previously, Applicants have described numerous embodiments of an MRI agent having a peptide moiety comprising an -Ala-Leu- group, such as on page 24 of the specification, specifically lines 33-40. The specification on page 24, lines 24-26 discloses that MRI agents having the -Ala-Leu- moiety can interact with MMP to cause a "chewing off" of the peptide. The specification thus provides "distinguishing identifying characteristics" sufficient to show that Applicants were in possession of the claimed invention.

The Examiner states that "while it is clear that applicant envisaged a few representative MMP recognizable peptide sequences and their conjugation to a DOTA macrocycle, such a few representative examples does not provide support that applicant had support for the millions and millions of possible sequences which may or may not be expected to have MMP recognition activity due to the drastic variety of structure/functional activity possibilities represented by such a genus." However, MPEP 2163(II)(A)(3)(a)(ii) provides that

> What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

As stated above, all of the peptide moieties share the common structural feature of an -Ala-Leu- moiety, and amino acids used to form $(Y_1)_n$ and $(Y_2)_m$ are known in the art. The Examiner has stated previously that "each Y_1 and Y_2 may independently represent 20^5 structures." However, Applicants submit that *all* of those structures can be determined by one of skill in the art, who would therefore recognize that Applicants had possession of the recited genus.

The specification thus provide adequate written description for the claims. Withdrawal of the rejection is therefore respectfully requested.

Rejection under 35 USC 102(e)

The Examiner has rejected claims 20, 22 and 29 under 35 USC 102(e) as allegedly being anticipated by Lauffer et al., US Patent 6,709,646.

Claim 20 has been amended to recite that the MMP active peptide is cleaved by interacting with an MMP such that the *q* value of said MRI agent is increased. Lauffer does not explicitly or inherently disclose this limitation. In Lauffer, changes in relaxivity are due to the change in rotational correlation time of an MRI contrast agent. Thus, Lauffer in column 3, lines 18-21, discloses that "[b]inding of the small-molecular-weight gadolinium chelates to large macromolecules slows the rotation tumbling time and increases the relaxation enhancement by factors of 3 to 10." When the rotational motions of the chelate are slowed, the magnetic fluctuations between the paramagnetic ion and water protons occur on the same time scale as the Larmor frequency of the protons, resulting in highly efficient coupling that greatly enhances relaxivity. See Lauffer, col. 13, lines 21-25. Thus, Lauffer teaches that relaxivity enhancements are due to changes in chelate motion when the chelate binds noncovalently to a target such as Human Serum Albumin (HSA). While Lauffer discloses cleavage at a modification site such as in Compound 1, such cleavage alone does not appear to result in higher relaxivity. Rather, cleavage facilitates the noncovalent binding of the cleaved molecule to a binding partner, which slows the rotational motion of the cleaved molecule and allows for matching of the magnetic fluctuations and hence greater relaxivity. See also, Lauffer, col. 4, lines 53-57, disclosing that "The MM [masking moiety] 'masks' (or decreases) the binding of the prodrug to the protein within the tissue to be imaged; once the MM is removed by cleavage at the MS [modification site], then the increased binding affinity of the agent is expressed." On the other hand, amended claim 20 recites that *q*, the number of coordination sites of the recited MRI agent, is increased when contacted with MMP.

As further evidence of why Applicants believe that *q* is not increased when the compounds of Lauffer are cleaved and subsequently bind to a target moiety, Applicants cite Caravan et al., *Journal of the American Chemical Society*, 2002, 124: 3152 (submitted herewith as Exhibit A), which is coauthored by R. Lauffer. Caravan is directed to MS-325, a DTPA chelate substituted with a *diphenyl*cyclohexyl serum albumin binding group. See Caravan, Chart 1. MS-325 is similar in structure to Compound 8 as disclosed by Lauffer in the '646 Patent and cited by the Examiner. Compound 8 comprises a DTPA chelate substituted with a *diphenyl* serum albumin binding group. The Examiner on pages 5 and 6 extrapolates the properties of Compound

8 to Compound 2, a DTPA chelate substituted with a purported MMP1 substrate peptide, and it is Compound 2 that appears to form the basis for the rejection under 102(e).

The abstract of Caravan discloses that "the Eu(III) analogue of MS-325 is shown to contain one inner-sphere water molecule *in the presence and in the absence* of HSA. . . . The high relaxivity of MS-325 bound to HSA is primarily because of a *60-100-fold increase in the rotational correlation time* of the molecule upon binding." See also Caravan, p. 3156, col. 2, ¶ 3 ("MS-325 has one coordinated water molecule *in either free PBS or when bound to HSA*."). Thus, Caravan discloses that enhanced relaxivity is due to slowed rotational motions, not a change in q since q of MS-325 is the same in both bound and unbound states. Given the structural similarities of MS-325 to Compound 8 of Lauffer, Applicants submit that the increased relaxivity upon cleavage of Compound 8 and by extension of Compound 2 is not due to an increase in q as recited in the amended claims.

Since Lauffer does not teach each and every element recited in the claims as amended, the claims are not anticipated. Withdrawal of the rejection is therefore respectfully requested.

Rejection under 35 USC 103

The Examiner has rejected claims 19-22 and 29 under 35 USC 103(a) as allegedly unpatentable over Lauffer et al. in view of Netzel-Arnett et al., Biochemistry, 1993, 32: 6427-6432.

As stated above, Lauffer does not disclose that q is increased after the chelate is cleaved. Netzel-Arnett, directed to peptides cleavable by MMP, does not cure this deficiency. Lauffer and Netzel-Arnett in combination therefore do not disclose or suggest all of the elements of the claims. The claims are therefore not obvious over the cited references and so withdrawal of the rejection is requested.

Conclusion

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1282 (direct line).

While Applicant believes that no fees are due at this time, the Commissioner is hereby authorized to charge any fees, including extension fees, or to credit any overpayment in connection with this reply to Deposit Account 50-0310 (Attorney Docket No. 068269-5010-US).

Respectfully submitted,

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